Published in final edited form as:

Curr Opin Rheumatol. 2016 November ; 28(6): 571–576. doi:10.1097/BOR.0000000000000333.

Aberrant Immune Response with Consequent Vascular and Connective Tissue Remodeling – Causal to Scleroderma and Associated Syndromes such as Raynaud Phenomenon and Other Fibrosing Syndromes ?

Nedim Durmus^{1,2}, Sung-Hyun Park¹, Joan Reibman^{1,2}, and Gabriele Grunig^{1,2}

¹Dept. Environmental Medicine, New York University Langone Medical Center, Tuxedo, NY, 10987, USA

²Dept. Medicine, New York University Langone Medical Center, Tuxedo, NY, 10987, USA

Abstract

Purpose of review—Scleroderma and other autoimmune induced connective tissue diseases are characterized by dysfunctions in the immune system, connective tissue and the vasculature. We are focusing on systemic sclerosis (SSc) associated pulmonary hypertension, which remains a leading cause of death with only a 50–60% two-year survival rate.

Recent findings—Much research and translational efforts have been directed at understanding the immune response that causes SSc and the networked interactions with the connective tissue and the vasculature. One of the unexpected findings was that in some cases the pathogenic immune response in SSc resembles the immune response to helminth parasites. During co-evolution, means of communication were developed which protect the host from over-colonization with parasites and which protect the parasite from excessive host responses. One explanation for the geographically clustered occurrence of SSc is that environmental exposures combined with genetic predisposition turn on triggers of molecular and cellular modules that were once initiated by parasites.

Summary—Future research is needed to further understand the parasite-derived signals that dampen the host response. Therapeutic helminth infection or treatment with parasite-derived response modifiers could be promising new management tools for autoimmune connective tissue diseases.

Keywords

immune responses; autoimmunity; pulmonary hypertension; helminth parasites; host-microbial communication

*Corresponding author: Gabriele Grunig, DVM, PhD, Department of Environmental Medicine & Medicine, New York University School of Medicine, 57 Old Forge Rd, Tuxedo New York 10987, Phone: 845-731-3669; FAX: 845-351-5472, ggrunig1@earthlink.net; gabriele.grunig@nyumc.org.

Conflicts of Interest: None declared.

Introduction

Connective tissue diseases including Raynaud's phenomenon, Systemic Sclerosis (SSc), and Systemic Lupus Erythematosus have an autoimmune component that leads to the production of autoantibodies, vascular disease and remodeling of the vasculature and the connective tissue [1]. The clinical problem can be localized to the hands and feet, or spread to further skin areas and internal organs [1]. SSc particularly when affecting internal organs has the worst prognosis with a decrease in life expectancy [2].

Genetic predisposition clearly points to the causative role of an aberrant immune response for these diseases. Genetic risk factors for SSc include for example specific major histocompatibility complex (MHC) haplotypes [3–6]. Virtually all cells in the body express MHC molecules to display peptides to the immune cells, specifically lymphocytes. Specific antigen presenting cells, i.e. dendritic cells, utilize the MHC molecules to specifically direct T- and B- lymphocytes. The interaction of these cells stimulates antibody production by B cells. Antibodies that are directed against autologous cell material are called autoantibodies. Autoantibodies can be biomarkers of a misdirected immune response [7,8], but can also directly cause the tissue dysfunction [9–11]. Agonistic autoantibodies that mimic the function of endothelin and angiotensin by binding to the respective receptors can cause the vasculopathy [9] and exacerbate the immune dysfunction [10] in SSc. These cell-receptor specific antibodies [9,11] join the nuclear anti-topoisomerase [12] antibodies for their pathogenic roles in SSc.

The associations between SSc and MHC haplotypes which are specific for certain ethnic groups, for example native American [3,4], Japanese [5], or Mexican [6] people may explain clinical endotypes of SSc and also gene by environment interactions. As mentioned above, MHC molecules display peptides to immune cells. Chemical exposures, including exposures to substances from the environment can cause protein modifications, e.g. nitration [13,14]. The nitration modification confers subtle changes to peptides which in turn are better displayed by certain MHC haplotypes, but not by others [14]. Confirmed environmental risk factors for SSc include exposures to silica, solvents, and certain work environments [15,16]. However, epidemiological studies of environmental exposures in SSc are hampered by the relatively low frequency of disease. The occurrence of geographic clustering of SSc [17,18] sometimes affecting specific ethnic groups [4,19,20] indicates that the role of environmental exposures for SSc maybe under-estimated.

The wide scope of the dysfunction of the immune response in SSc renders the treatment of the condition challenging. This is reflected by the breadth of targets of interventions that are currently at the clinical trial stage for SSc. Ongoing clinical trials for SSc are registered worldwide at the clinicaltrials.gov site with the majority being performed in the United States (36) and Europe (43). Organ specific disease management makes up the largest percentage, followed by trials to identify diagnostics and biomarkers. Patient support (registries, advocacy), and drugs targeting the vasculature & coagulation, cell ablation & cell / tissue transplantation, as well as drugs targeting the immune response / vaccine / microbial reconstitution make up the majority of the other trials.

Pulmonary hypertension in SSc

Pulmonary fibrosis, pulmonary hypertension, cardiac disease and kidney disease as well as early onset Raynaud's phenomenon are predictors of mortality in SSc [2]. The two-year survival rate of SSc associated pulmonary hypertension (PH) is at an estimated 50–60 percentage, despite the availability of treatment for PH [2,21,22]. Mean pulmonary artery pressures that are at the high end of the normal range (21–24 mmHg) are considered borderline PH [23]. Borderline PH is considered a risk factor for worsening of the SSc syndrome that may ultimately lead to overt SSc associated PH [23].

Immune response induced pulmonary hypertension, a vexing biological question

Pulmonary hypertension (PH) is characterized by the increase of the pulmonary artery pressure associated with remodeling and constriction of the pulmonary arteries, increased right heart pressure and remodeling of the right heart [24]. The immune response is thought to play a critical part in the development of SSc associated PH [25,26]. Different immune response subtypes are associated with SSc associated PH, including the T helper 2 (Th2) response [25,27,28], Th17 response [25,29] and also the Th1-Interferon response [28]. The Th2 and Th17 responses are thought to have organ-independent pro-fibrotic roles by interacting with fibroblasts and thereby contributing to SSc [25]. In support of this notion the Th2 cytokine, Interleukin (IL)-13, has been shown to cause dermal fibrosis in SSc by affecting the skin where it is produced by CD8+ lymphocytes [30]. Studies in mice using experimental skin fibrosis models support the pro-fibrotic role of IL-13 [31,32].

Experimental studies in mice have shown that a T helper 2 (Th2) immune response can cause severe pulmonary arterial remodeling [33–35]. Further studies revealed that this response is exacerbated by urban particulate matter (PM_{2.5}) from air pollution [36]. In this case, both pulmonary arterial remodeling and increased right ventricular systolic pressure are induced. Further studies showed that IL-13 and IL-17A are involved in developing the pulmonary hypertension phenotype induced by antigen and particulate matter (Fig. 1) [37]. Simultaneous blocking of IL-13 and IL-17A significantly reduced right ventricular pressures [37]. Further, we showed that B cells were necessary for the development of increased right ventricular pressures and molecular changes in the right heart in response to sensitization and intranasal challenge with antigen and particulate matter (Fig. 1) [38]. In this case, the increase in right ventricular systolic pressure and right ventricular molecular changes were restored by reconstituting the B cell KO mice with antigen specific IgG1[38]. Together, the data show that the immune response is sufficient to induce the pulmonary hypertension phenotype, as schematically shown in Figure 1. The questions are: why would the biological response be set up in this particular manner, and why would the immune response that can cause the pulmonary hypertension phenotype be reminiscent of the response that causes the asthma phenotype?

Parasites induced pulmonary hypertension

Schistosomiasis-associated pulmonary hypertension is driven by the inflammation and host response to parasite antigens. Schistosomiasis is the third most common parasitic disease affecting about 200 to 300 million people in 74 countries including throughout Africa, Brazil, the Middle East and Southeast Asia [39]. Schistosomiasis is an ancient and chronic disease of humans, mammal, birds, and primates. The first host response to antigens released by these worms is a Th-1 response during acute infection [39]. The host releases tumor necrosis factor (TNF) α , interleukin (IL)-1, IL-6, IL-12[40,41], transforming growth factor (TGF) β and interferon- γ [42–44]. However, during chronic infection, schistosome eggs and egg-derived antigens released by worms migrate to lungs and induce a Th2 response. The Th2 milieu induces tissue-remodeling cytokines such as IL-4 [33–35], IL-13 [33,35], and resistin-like molecule α (RELMA α) [34,45,46]. The immune response to the parasite eggs and their antigens together with exacerbated activity of TGF- β induce severe pulmonary arterial remodeling and pulmonary hypertension [35,39,44,47,48] (Fig. 1).

Parasite – host communication

Factors (protein, sugar, cytokines) produced by the parasites

The antigens released by parasites induce host immune response and cause host disease. However, to help shared survival, of host and parasites, the parasites produce several factors (e.g. protein, sugar, cytokines) that can modulate the immune response.

Sugars

Lacto-N-fucopentaose III (LNFPIII) is the sugar found in both parasitic helminths and human milk. Several recent reports showed that LNFPIII from soluble egg antigen also modulate immune response [49]. The protective role of LNFPIII for host is to alleviate hepatosteatosis and insulin resistance [50]. LNFPIII induces alternative macrophage activation and up-regulates the expression of arginase 1 and chitinase-like 3 (Chil3-Ym1) [51]. These alternative macrophage signals protect the host against organ injury through down-regulation of egg-induced inflammation [52]. LNFPIII also induces IL-10, up-regulates T regulatory cells and inhibits inflammatory responses induced by bacterial lipopolysaccharide [53].

Growth factor receptor signaling

During intestinal infection with nematode parasites (such as *Trichuris muris*), the host produces a Th2 immune response for protection against the parasite [54] and induces epidermal growth factor (EGF) family cytokines to proliferate the gut epithelium [55]. For example, epidermal growth factor-like cytokine Amphiregulin (AREG) that is produced as consequence of the Th2 response leads to increased proliferation of the gut epithelium and enhances parasite clearance [56]. Furthermore, AREG enhances the function of T regulatory cells which function is to restrict the magnitude of the immune response [57].

Cytokines

The eggs produced by Schistosomes during chronic infection cause granulomas and fibrotic disease. Therefore, egg production by the parasite is critical for pathogenesis. TGF- β signaling plays an important role in the embryogenesis of the parasite. The schistosome-genome has several components of the TGF- β pathway including type I receptor, *Schistosoma mansoni* receptor kinase-1 (SmRK1) [58], type II receptor (SmRK2) [59], as well as the signaling molecules downstream of the receptor, the Smad homologues [60–62]. Further, the mammalian host ligand, TGF- β , can signal in the parasite's TGF- β pathway [63]. Additionally, one report identified the parasite ligand, a parasite-encoded TGF- β superfamily member, *Schistosoma mansoni* Inhibin/Activin (SmInAct). SmInAct is thought to be critically important for the production of eggs, and this process also involves the immune response by the mammalian host [64].

Helminth treatment

In western countries and industrialized countries in which the incidence of helminth infection is reduced, there is an increased frequency of immunological diseases including inflammatory bowel disease, asthma, other allergic disease and autoimmune disease [65–67]. Helminths have preceded mammals during evolution, not only in the free-living stage but also as parasites of invertebrates [68], plants [69] and other hosts [70]. Mammals including humans [71] co-evolved with helminths [69] presumably resulting in an adapted response system for symbiosis / parasitism with helminths [72]. The mammalian host had to establish protective mechanisms directed against the parasites. For example Schistosome cercariae enter via the skin and thickened skin is a better barrier [73]. Further, thickened pulmonary arteries have decreased permeability [74], a change that would protect from intravascular parasites.

Conversely, by the elimination of parasite infection, the mammalian host lost the communication network with the parasite. As explained above, the host-parasite communication included cues that regulate the homeostasis of many organs including the vasculature, connective tissue and the immune system. The loss of this communication is thought to contribute to the high incidence of immunological diseases [75,76]. Therefore, a current idea states that helminth infection could protect the host against severe auto-inflammatory events while causing parasitism and mild to moderate disease [77]. Proof-of-concept studies have explored exposure to helminths for therapy of immune-mediated diseases. For example, helminth treatment reduced the symptoms of inflammatory bowel disease by inducing immune-regulatory networks and mucosal repair and by altering communities of microbiome within the intestinal tract [67,78].

Conclusion

Hypothesis of the missing parasite-host interaction in autoimmunity associated PH

A tantalizing hypothesis is that cues from the environment, in combination with chronic exposure to antigen, or chronic infection mimic the presence of a helminth infection, although there is no helminth parasite present in the host (Fig. 1). The missing communication cues from the helminth to the mammalian host can cause exacerbated and

uncontrolled immune responses, which in turn can cause wide spread vasculopathy and fibrosis, including the pulmonary arteries. It follows that treatment with medical helminths or with soluble communication mediators that would be secreted by the helminths if there were infection, could provide novel means of intervention for SSc, SSc associated PH and other autoimmune connective tissue diseases.

Acknowledgments

Sources of support: The work was funded in part by the National Institutes of Health 1R21HL092370-01 (GG), 1R01 HL095764-01 (GG); American Heart Association, Founders affiliate (0855943D, GG); TUBITAK (1059B191401602 ND) and Hacettepe University (014 G 602 002 ND)

References Cited

1. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, Matucci-Cerinic M, Naden RP, Medsger TA Jr, Carreira PE, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis*. 2013; 72:1747–1755. [PubMed: 24092682]
2. Tyndall AJ, Bannert B, Vonk M, Airo P, Cozzi F, Carreira PE, Bancel DF, Allanore Y, Muller-Ladner U, Distler O, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis*. 2010; 69:1809–1815. [PubMed: 20551155]
3. Tan FK, Stivers DN, Arnett FC, Chakraborty R, Howard R, Reveille JD. HLA haplotypes and microsatellite polymorphisms in and around the major histocompatibility complex region in a Native American population with a high prevalence of scleroderma (systemic sclerosis). *Tissue Antigens*. 1999; 53:74–80. [PubMed: 10082433]
4. Arnett FC, Howard RF, Tan F, Moulds JM, Bias WB, Durban E, Cameron HD, Paxton G, Hodge TJ, Weathers PE, et al. Increased prevalence of systemic sclerosis in a Native American tribe in Oklahoma. Association with an Amerindian HLA haplotype. *Arthritis Rheum*. 1996; 39:1362–1370. [PubMed: 8702445]
5. Furukawa H, Oka S, Kawasaki A, Shimada K, Sugii S, Matsushita T, Hashimoto A, Komiya A, Fukui N, Kobayashi K, et al. Human Leukocyte Antigen and Systemic Sclerosis in Japanese: The Sign of the Four Independent Protective Alleles, DRB1*13:02, DRB1*14:06, DQB1*03:01, and DPB1*02:01. *PLoS One*. 2016; 11:e0154255. [PubMed: 27116456] beautiful example of molecular ethnic cluster of systemic sclerosis
6. Rodriguez-Reyna TS, Mercado-Velazquez P, Yu N, Alosco S, Ohashi M, Lebedeva T, Cruz-Lagunas A, Nunez-Alvarez C, Cabiedes-Contreras J, Vargas-Alarcon G, et al. HLA Class I and II Blocks Are Associated to Susceptibility, Clinical Subtypes and Autoantibodies in Mexican Systemic Sclerosis (SSc) Patients. *PLoS One*. 2015; 10:e0126727. [PubMed: 25993664] beautiful example of molecular ethnic cluster of systemic sclerosis
7. Becker MO, Kill A, Kutsche M, Guenther J, Rose A, Tabeling C, Witzernath M, Kuhl AA, Heidecke H, Ghofrani HA, et al. Vascular receptor autoantibodies in pulmonary arterial hypertension associated with systemic sclerosis. *Am J Respir Crit Care Med*. 2014; 190:808–817. [PubMed: 25181620]
8. Hinchcliff M, Khanna S, Hsu VM, Lee J, Almagor O, Chang RW, Steen V, Chung L, Investigators P. Survival in systemic sclerosis-pulmonary arterial hypertension by serum autoantibody status in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) Registry. *Semin Arthritis Rheum*. 2015; 45:309–314. [PubMed: 26210782] important scleroderma registry
9. Kill A, Tabeling C, Undeutsch R, Kuhl AA, Gunther J, Radic M, Becker MO, Heidecke H, Worm M, Witzernath M, et al. Autoantibodies to angiotensin and endothelin receptors in systemic sclerosis induce cellular and systemic events associated with disease pathogenesis. *Arthritis Res Ther*. 2014; 16:R29. [PubMed: 24472528]

10. Gunther J, Kill A, Becker MO, Heidecke H, Rademacher J, Siegert E, Radic M, Burmester GR, Dragun D, Riemekasten G. Angiotensin receptor type 1 and endothelin receptor type A on immune cells mediate migration and the expression of IL-8 and CCL18 when stimulated by autoantibodies from systemic sclerosis patients. *Arthritis Res Ther*. 2014; 16:R65. [PubMed: 24612997]
11. Cabral-Marques O, Riemekasten G. Vascular hypothesis revisited: Role of stimulating antibodies against angiotensin and endothelin receptors in the pathogenesis of systemic sclerosis. *Autoimmun Rev*. 2016; 15:690–694. [PubMed: 26970493] beautiful summary of the function of agonistic receptor specific autoantibodies
12. Ochoa E, Martin JE, Assasi S, Beretta L, Carreira P, Guillen A, Simeon CP, Koumakis E, Dieude P, Allanore Y, et al. Confirmation of CCR6 as a risk factor for anti-topoisomerase I antibodies in systemic sclerosis. *Clin Exp Rheumatol*. 2015; 33:S31–S35. association of CCR6 gene polymorphisms thought to be important for IL-17-autoimmune responses and specific autoantibody response
13. Seimetz M, Parajuli N, Pichl A, Veit F, Kwapiszewska G, Weisel FC, Milger K, Egemnazarov B, Turowska A, Fuchs B, et al. Inducible NOS inhibition reverses tobacco-smoke-induced emphysema and pulmonary hypertension in mice. *Cell*. 2011; 147:293–305. [PubMed: 22000010]
14. Karle AC, Oostingh GJ, Mutschlechner S, Ferreira F, Lackner P, Bohle B, Fischer GF, Vogt AB, Duschl A. Nitration of the pollen allergen bet v 1.0101 enhances the presentation of bet v 1-derived peptides by HLA-DR on human dendritic cells. *PLoS One*. 2012; 7:e31483. [PubMed: 22348091]
15. Marie I, Menard JF, Duval-Modeste AB, Joly P, Dominique S, Bravard P, Noel D, Gehanno JF, Bubenheim M, Benichou J, et al. Association of occupational exposure with features of systemic sclerosis. *J Am Acad Dermatol*. 2015; 72:456–464. [PubMed: 25582539] careful review of the knowledge about the role of environmental exposures for systemic sclerosis
16. Marie I, Gehanno JF, Bubenheim M, Duval-Modeste AB, Joly P, Dominique S, Bravard P, Noel D, Cailleux AF, Weber J, et al. Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature. *Autoimmun Rev*. 2014; 13:151–156. [PubMed: 24129037]
17. Meyer A, Chiffot H, Chatelus E, Kleinmann JF, Ronde-Ousteu C, Klein D, Jegu J, Geny B, Hirshi S, Canuet M, et al. Brief Report: Spatial Heterogeneity of Systemic Sclerosis in France: High Prevalence in the Northeast Region. *Arthritis Rheumatol*. 2016; 68:1731–1737. [PubMed: 26816302] manuscript highlights geographical clustering of systemic sclerosis
18. Gregory AC 2nd, Shendell DG, Okosun IS, Gieseke KE. Multiple Sclerosis disease distribution and potential impact of environmental air pollutants in Georgia. *Sci Total Environ*. 2008; 396:42–51. [PubMed: 18433841]
19. Low AH, Johnson SR, Lee P. Ethnic influence on disease manifestations and autoantibodies in Chinese-descent patients with systemic sclerosis. *J Rheumatol*. 2009; 36:787–793. [PubMed: 19228652]
20. Blanco I, Mathai S, Shafiq M, Boyce D, Kolb TM, Chami H, Hummers LK, Houston T, Chaisson N, Zaiman AL, et al. Severity of systemic sclerosis-associated pulmonary arterial hypertension in African Americans. *Medicine (Baltimore)*. 2014; 93:177–185. [PubMed: 25181310]
21. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. *Ann Rheum Dis*. 2007; 66:940–944. [PubMed: 17329309]
22. Chung L, Farber HW, Benza R, Miller DP, Parsons L, Hassoun PM, McGoon M, Nicolls MR, Zamanian RT. Unique predictors of mortality in patients with pulmonary arterial hypertension associated with systemic sclerosis in the REVEAL registry. *Chest*. 2014; 146:1494–1504. [PubMed: 24992469]
23. Visovatti SH, Distler O, Coghlan JG, Denton CP, Grunig E, Bonderman D, Muller-Ladner U, Pope JE, Vonk MC, Seibold JR, et al. Borderline pulmonary arterial pressure in systemic sclerosis patients: a post-hoc analysis of the DETECT study. *Arthritis Res Ther*. 2014; 16:493. [PubMed: 25491468]
24. Rabinovitch M. Molecular pathogenesis of pulmonary arterial hypertension. *J Clin Invest*. 2012; 122:4306–4313. [PubMed: 23202738]
25. O'Reilly S, Hogle T, van Laar JM. T cells in systemic sclerosis: a reappraisal. *Rheumatology (Oxford)*. 2012; 51:1540–1549. [PubMed: 22577083]

26. Gashouta MA, Humbert M, Hassoun PM. Update in systemic sclerosis-associated pulmonary arterial hypertension. *Presse Med.* 2014; 43:e293–e304. [PubMed: 25179278]
27. Greenblatt MB, Sargent JL, Farina G, Tsang K, Lafyatis R, Glimcher LH, Whitfield ML, Aliprantis AO. Interspecies comparison of human and murine scleroderma reveals IL-13 and CCL2 as disease subset-specific targets. *Am J Pathol.* 2012; 180:1080–1094. [PubMed: 22245215]
28. Christmann RB, Hayes E, Pendergrass S, Padilla C, Farina G, Affandi AJ, Whitfield ML, Farber HW, Lafyatis R. Interferon and alternative activation of monocyte/macrophages in systemic sclerosis-associated pulmonary arterial hypertension. *Arthritis Rheum.* 2011; 63:1718–1728. [PubMed: 21425123]
29. Radstake TR, van Bon L, Broen J, Hussiani A, Hesselstrand R, Wuttge DM, Deng Y, Simms R, Lubberts E, Lafyatis R. The pronounced Th17 profile in systemic sclerosis (SSc) together with intracellular expression of TGFbeta and IFNgamma distinguishes SSc phenotypes. *PLoS One.* 2009; 4:e5903. [PubMed: 19536281]
30. Fuschiotti P, Larregina AT, Ho J, Feghali-Bostwick C, Medsger TA Jr. Interleukin-13-producing CD8+ T cells mediate dermal fibrosis in patients with systemic sclerosis. *Arthritis Rheum.* 2013; 65:236–246. [PubMed: 23001877]
31. Fernandez P, Trzaska S, Wilder T, Chiriboga L, Blackburn MR, Cronstein BN, Chan ES. Pharmacological blockade of A2A receptors prevents dermal fibrosis in a model of elevated tissue adenosine. *Am J Pathol.* 2008; 172:1675–1682. [PubMed: 18467695]
32. Aliprantis AO, Wang J, Fathman JW, Lemaire R, Dorfman DM, Lafyatis R, Glimcher LH. Transcription factor T-bet regulates skin sclerosis through its function in innate immunity and via IL-13. *Proc Natl Acad Sci U S A.* 2007; 104:2827–2830. [PubMed: 17307869]
33. Daley E, Emson C, Guignabert C, de Waal Malefyt R, Louten J, Kurup VP, Hogaboam C, Taraseviciene-Stewart L, Voelkel NF, Rabinovitch M, et al. Pulmonary arterial remodeling induced by a Th2 immune response. *J Exp Med.* 2008; 205:361–372. [PubMed: 18227220]
34. Yamaji-Kegan K, Takimoto E, Zhang A, Weiner NC, Meuchel LW, Berger AE, Cheadle C, Johns RA. Hypoxia-induced mitogenic factor (FIZZ1/RELMalpha) induces endothelial cell apoptosis and subsequent interleukin-4-dependent pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol.* 2014; 306:L1090–L1103. [PubMed: 24793164]
35. Kumar R, Mickael C, Chabon J, Gebreab L, Rutebemberwa A, Rodriguez Garcia A, Koyanagi DE, Sanders L, Gandjeva A, Kearns MT, et al. The causal role of IL-4 and IL-13 in *Schistosoma mansoni* Pulmonary Hypertension. *Am J Respir Crit Care Med.* 2015 study demonstrates the surprising collaborative roles of IL-4 and IL-13 for *Schistosoma* induced pulmonary hypertension phenotype
36. Grunig G, Marsh LM, Esmail N, Jackson K, Gordon T, Reibman J, Kwapiszewska G, Park SH. Perspective: ambient air pollution: inflammatory response and effects on the lung's vasculature. *Pulm Circ.* 2014; 4:25–35. [PubMed: 25006418]
37. Park SH, Chen WC, Esmail N, Lucas BEG, Marsh LM, Reibman J, Grunig G. IL-13 and IL-17A induced pulmonary-hypertension-phenotype due to inhalation of antigen and fine particles from air pollution. *Pulm Circ.* 2014; 4:654–668. [PubMed: 25610601]
38. Park SH, Chen WC, Durmus N, Bleck B, Reibman J, Riemekasten G, Grunig G. The effects of antigen-specific IgG1 antibody for the pulmonary-hypertension-phenotype and B cells for inflammation in mice exposed to antigen and fine particles from air pollution. *PLoS One.* 2015; 10:e0129910. [PubMed: 26079807] study demonstrates the surprising roles of B cells and IgG1 for the experimental pulmonary hypertension phenotype
39. Graham BB, Bandeira AP, Morrell NW, Butrous G, Tudor RM. Schistosomiasis-associated pulmonary hypertension: pulmonary vascular disease: the global perspective. *Chest.* 2010; 137:20S–29S. [PubMed: 20522577]
40. Duraes FV, Carvalho NB, Melo TT, Oliveira SC, Fonseca CT. IL-12 and TNF-alpha production by dendritic cells stimulated with *Schistosoma mansoni* schistosomula tegument is TLR4- and MyD88-dependent. *Immunol Lett.* 2009; 125:72–77. [PubMed: 19539649]
41. Wynn TA, Cheever AW, Jankovic D, Poindexter RW, Caspar P, Lewis FA, Sher A. An IL-12-based vaccination method for preventing fibrosis induced by schistosome infection. *Nature.* 1995; 376:594–596. [PubMed: 7637808]

42. de Jesus AR, Silva A, Santana LB, Magalhaes A, de Jesus AA, de Almeida RP, Rego MA, Burattini MN, Pearce EJ, Carvalho EM. Clinical and immunologic evaluation of 31 patients with acute schistosomiasis mansoni. *J Infect Dis.* 2002; 185:98–105. [PubMed: 11756987]
43. Boros DL, Whitfield JR. Enhanced Th1 and dampened Th2 responses synergize to inhibit acute granulomatous and fibrotic responses in murine schistosomiasis mansoni. *Infect Immun.* 1999; 67:1187–1193. [PubMed: 10024559]
44. Graham BB, Chabon J, Gebreab L, Poole J, Debella E, Davis L, Tanaka T, Sanders L, Dropcho N, Bandeira A, et al. Transforming growth factor-beta signaling promotes pulmonary hypertension caused by *Schistosoma mansoni*. *Circulation.* 2013; 128:1354–1364. [PubMed: 23958565]
45. Liu T, Yu H, Ullenbruch M, Jin H, Ito T, Wu Z, Liu J, Phan SH. The in vivo fibrotic role of FIZZ1 in pulmonary fibrosis. *PLoS One.* 2014; 9:e88362. [PubMed: 24516640]
46. Angelini DJ, Su Q, Yamaji-Kegan K, Fan C, Skinner JT, Champion HC, Crow MT, Johns RA. Hypoxia-induced mitogenic factor (HIMF/FIZZ1/RELMalpha) induces the vascular and hemodynamic changes of pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol.* 2009; 296:L582–L593. [PubMed: 19136574]
47. El Kasmi KC, Pugliese SC, Riddle SR, Poth JM, Anderson AL, Frid MG, Li M, Pullamsetti SS, Savai R, Nagel MA, et al. Adventitial fibroblasts induce a distinct proinflammatory/profibrotic macrophage phenotype in pulmonary hypertension. *J Immunol.* 2014; 193:597–609. [PubMed: 24928992]
48. Graham BB, Chabon J, Bandeira A, Espinheira L, Butrous G, Tudor RM. Significant intrapulmonary *Schistosoma* egg antigens are not present in schistosomiasis-associated pulmonary hypertension. *Pulm Circ.* 2011; 1:456–461. [PubMed: 22530100]
49. Srivastava L, Tundup S, Choi BS, Norberg T, Harn D. Immunomodulatory glycan lacto-N-fucopentaose III requires clathrin-mediated endocytosis to induce alternative activation of antigen-presenting cells. *Infect Immun.* 2014; 82:1891–1903. [PubMed: 24566617]
50. Bhargava P, Li C, Stanya KJ, Jacobi D, Dai L, Liu S, Gangl MR, Harn DA, Lee CH. Immunomodulatory glycan LNFPIII alleviates hepatosteatosis and insulin resistance through direct and indirect control of metabolic pathways. *Nat Med.* 2012; 18:1665–1672. [PubMed: 23104131]
51. Atochina O, Da'dara AA, Walker M, Harn DA. The immunomodulatory glycan LNFPIII initiates alternative activation of murine macrophages in vivo. *Immunology.* 2008; 125:111–121. [PubMed: 18373667]
52. Herbert DR, Holscher C, Mohrs M, Arendse B, Schwegmann A, Radwanska M, Leeto M, Kirsch R, Hall P, Mossmann H, et al. Alternative macrophage activation is essential for survival during schistosomiasis and downmodulates T helper 1 responses and immunopathology. *Immunity.* 2004; 20:623–635. [PubMed: 15142530]
53. Harn DA, McDonald J, Atochina O, Da'dara AA. Modulation of host immune responses by helminth glycans. *Immunol Rev.* 2009; 230:247–257. [PubMed: 19594641]
54. Cliffe LJ, Grecis RK. The *Trichuris muris* system: a paradigm of resistance and susceptibility to intestinal nematode infection. *Adv Parasitol.* 2004; 57:255–307. [PubMed: 15504540]
55. Potten CS, Owen G, Hewitt D, Chadwick CA, Hendry H, Lord BI, Woolford LB. Stimulation and inhibition of proliferation in the small intestinal crypts of the mouse after in vivo administration of growth factors. *Gut.* 1995; 36:864–873. [PubMed: 7615275]
56. Zaiss DM, Yang L, Shah PR, Kobie JJ, Urban JF, Mosmann TR. Amphiregulin, a TH2 cytokine enhancing resistance to nematodes. *Science.* 2006; 314:1746. [PubMed: 17170297]
57. Zaiss DM, van Loosdregt J, Gorlani A, Bekker CP, Grone A, Sibilia M, van Bergen en Henegouwen PM, Roovers RC, Coffey PJ, Sijts AJ. Amphiregulin enhances regulatory T cell-suppressive function via the epidermal growth factor receptor. *Immunity.* 2013; 38:275–284. [PubMed: 23333074]
58. Davies SJ, Shoemaker CB, Pearce EJ. A divergent member of the transforming growth factor beta receptor family from *Schistosoma mansoni* is expressed on the parasite surface membrane. *J Biol Chem.* 1998; 273:11234–11240. [PubMed: 9556614]
59. Forrester SG, Warfel PW, Pearce EJ. Tegumental expression of a novel type II receptor serine/threonine kinase (SmRK2) in *Schistosoma mansoni*. *Mol Biochem Parasitol.* 2004; 136:149–156. [PubMed: 15478794]

60. Osman A, Niles EG, LoVerde PT. Identification and characterization of a Smad2 homologue from *Schistosoma mansoni*, a transforming growth factor-beta signal transducer. *J Biol Chem*. 2001; 276:10072–10082. [PubMed: 11152451]
61. Osman A, Niles EG, LoVerde PT. Expression of functional *Schistosoma mansoni* Smad4: role in Erk-mediated transforming growth factor beta (TGF-beta) down-regulation. *J Biol Chem*. 2004; 279:6474–6486. [PubMed: 14630909]
62. Beall MJ, McGonigle S, Pearce EJ. Functional conservation of *Schistosoma mansoni* Smads in TGF-beta signaling. *Mol Biochem Parasitol*. 2000; 111:131–142. [PubMed: 11087923]
63. Beall MJ, Pearce EJ. Human transforming growth factor-beta activates a receptor serine/threonine kinase from the intravascular parasite *Schistosoma mansoni*. *J Biol Chem*. 2001; 276:31613–31619. [PubMed: 11406634]
64. Freitas TC, Jung E, Pearce EJ. TGF-beta signaling controls embryo development in the parasitic flatworm *Schistosoma mansoni*. *PLoS Pathog*. 2007; 3:e52. [PubMed: 17411340]
65. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med*. 2002; 347:911–920. [PubMed: 12239261]
66. Hernandez JL, Leung G, McKay DM. Cestode regulation of inflammation and inflammatory diseases. *Int J Parasitol*. 2013; 43:233–243. [PubMed: 23058631]
67. Ramanan D, Bowcutt R, Lee SC, Tang MS, Kurtz ZD, Ding Y, Honda K, Gause WC, Blaser MJ, Bonneau RA, et al. Helminth infection promotes colonization resistance via type 2 immunity. *Science*. 2016; 352:608–612. [PubMed: 27080105] proof of concept study to show beneficial effects of medical helminth infection for mammalian host
68. Torchin ME, Miura O, Hechinger RF. Parasite species richness and intensity of interspecific interactions increase with latitude in two wide-ranging hosts. *Ecology*. 2015; 96:3033–3042. [PubMed: 27070022] snail hosts of helminth parasites
69. Poinar GO Jr. The Geological Record of Parasitic Nematode Evolution. *Adv Parasitol*. 2015; 90:53–92. [PubMed: 26597065] easy to understand outline of parasitic nematode evolution with view of the hosts
70. De Baets K, Littlewood DT. The Importance of Fossils in Understanding the Evolution of Parasites and Their Vectors. *Adv Parasitol*. 2015; 90:1–51. [PubMed: 26597064] evaluates the potential of the fossile record to understand the evolution of parasitism
71. Araujo A, Reinhard K, Ferreira LF. Palaeoparasitology - Human Parasites in Ancient Material. *Adv Parasitol*. 2015; 90:349–387. [PubMed: 26597072] parasites found in human archaeological material
72. De Baets K, Dentzien-Dias P, Upeniece I, Verneau O, Donoghue PC. Constraining the Deep Origin of Parasitic Flatworms and Host-Interactions with Fossil Evidence. *Adv Parasitol*. 2015; 90:93–135. [PubMed: 26597066] fossil studies with specific focus on the evolution of parasitism in flatworms (trematodes); schistosomes are flatworms
73. Palm NW, Rosenstein RK, Medzhitov R. Allergic host defences. *Nature*. 2012; 484:465–472. [PubMed: 22538607]
74. Tigani B, Cannet C, Karmouty-Quintana H, Ble FX, Zurbrugg S, Schaeublin E, Fozard JR, Beckmann N. Lung inflammation and vascular remodeling after repeated allergen challenge detected noninvasively by MRI. *Am J Physiol Lung Cell Mol Physiol*. 2007; 292:L644–L653. [PubMed: 17085517]
75. Weinstock JV. Helminths and mucosal immune modulation. *Ann N Y Acad Sci*. 2006; 1072:356–364. [PubMed: 17057216]
76. Ince MN, Elliott DE, Setiawan T, Metwali A, Blum A, Chen HL, Urban JF, Flavell RA, Weinstock JV. Role of T cell TGF-beta signaling in intestinal cytokine responses and helminthic immune modulation. *Eur J Immunol*. 2009; 39:1870–1878. [PubMed: 19544487]
77. Kuijk LM, van Die I. Worms to the rescue: can worm glycans protect from autoimmune diseases? *IUBMB Life*. 2010; 62:303–312. [PubMed: 20101628]
78. Broadhurst MJ, Ardeshir A, Kanwar B, Mirpuri J, Gundra UM, Leung JM, Wiens KE, Vujkovic-Cvijin I, Kim CC, Yarovsky F, et al. Therapeutic helminth infection of macaques with idiopathic chronic diarrhea alters the inflammatory signature and mucosal microbiota of the colon. *PLoS Pathog*. 2012; 8:e1003000. [PubMed: 23166490]

79. Graham BB, Mentink-Kane MM, El-Haddad H, Purnell S, Zhang L, Zaiman A, Redente EF, Riches DW, Hassoun PM, Bandeira A, et al. Schistosomiasis-induced experimental pulmonary hypertension: role of interleukin-13 signaling. *Am J Pathol.* 2010; 177:1549–1561. [PubMed: 20671265]
80. Graham BB, Kumar R. Schistosomiasis and the pulmonary vasculature (2013 Grover Conference series). *Pulm Circ.* 2014; 4:353–362. [PubMed: 25621148]

Key points

- Connective tissue diseases including the sclerosis associated disease spectrum can have severe clinical consequences particularly when associated with changes in multiple organs, for example systemic sclerosis (SSc) associated pulmonary hypertension.
- Under-appreciated gene by environment interactions could be the basis for the breath of dysfunction of the immune system, the vasculature and the connective tissue in SSc.
- These dysregulated responses may have their evolutionary history from response modules used in the communication between the mammalian host and parasitic helminths.
- Because the helminth vascular microbiome is missing in a large aspect of the population in westernized countries, the balancing and regulatory cues from helminth parasites are missing thus contributing to the development of the devastating Sclerosis spectrum connective tissue diseases.

**Helminth Parasite
(Schistosome eggs)**

Th2 response /
IL-13 & IL-4

Antigen & PM2.5
Th2-Th17 response /
IL-13, IL-17, IgG1
antibody

**severe pulmonary
arterial remodeling &
increase in right
ventricular
systolic
pressure**

Figure 1.

Schematic representation of the similarity of the immune mechanisms that induce severe thickening of the pulmonary artery and increases in right ventricular systolic pressure in response to infection with helminth parasites or exposure with antigen and ambient, urban fine dust (PM2.5).

The similarities of the changes in histology (severe pulmonary artery remodeling), physiology (right ventricular systolic pressure), and critical immune cytokines - IL-13 either combined with IL-4 (Schistosome eggs [35]) or IL-17A (antigen & PM2.5 [37]) - are particularly noteworthy. The changes in the lungs and hearts of SSc patients are remarkably similar and cytokine associations have been found that indicate involvements of IL-13 [27,28], IL-4 [28], IL-17A [29] or Interferon [28].

The data schematically represented above were generated using experimental mouse models [33,35,37,79] using cytokine-neutralizing antibodies and KO-mice. It is emphasized that the incidence of clinical pulmonary hypertension associated with Schistosomiasis infection in humans is still not fully known but is estimated at 6–7 % of all infected persons [80]. Two observations are clinically important: A) PH associated with Schistosomiasis generally fails to improve by only giving anti-helminthic treatment [80], emphasizing the significance of the host (immune) response for developing clinical signs of PH. B) A majority of

Schistosome infected individuals do not develop PH, indicating the strength of the cross-adaptation between the human host and the helminth parasite.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript